REVIEW MANAGEMENT

IND Process and Review Procedures

CONTENTS

PURPOSE This Guide describes:

- Policies and procedures for issuing and overseeing clinical holds to Investigational New Drug applications (INDs) and
- General review principles for INDs.

REFERENCES

Guidance for Industry: Content and Format of Phase 1 Investigational New Drug Applications (INDs) For Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products.

DEFINITIONS

- **Clinical Hold.** An order issued by FDA to the sponsor of an IND to delay or to suspend a clinical investigation.

- **Complete Clinical Hold.** A clinical hold that represents a hold of all clinical work requested under the IND.

- **Partial Clinical Hold.** A clinical hold of only part of the clinical work requested under the IND. [e.g. a specific protocol is not allowed to proceed; however, other protocols are allowed to proceed under the IND]. If only part of a protocol is allowed to be conducted, with progress to the next part contingent upon FDA review/approval of additional data, this is a partial hold. In contrast, if the division has told a sponsor that the sponsor needs to review results of a clinical study (or pre-clinical data) before proceeding, there is no hold.

- **Division.** All references to divisions or to division directors, reviewers, project managers, etc. are to new drug review divisions (ODE's) unless otherwise specified.

POLICY **General**

- The regulations [21 CFR 312.42(c)] require that where FDA concludes there may be grounds for imposing a clinical hold, FDA will "attempt to discuss and satisfactorily resolve the matter with the sponsor before issuing the clinical hold order." CDER experience is that most potential holds, particularly those based on inadequate patient monitoring, can be resolved through such discussion.

- The "General Review Principles" and "Responsibilities and Procedures" outlined below should be followed for all INDs.

Authority

- Authority to impose clinical holds on INDs has been delegated to division directors or acting division directors. This authority cannot be further delegated.

- Authority to discuss the planned protocol and modify it to resolve safety concerns is delegated to the medical team leader. If, however, safety concerns cannot be resolved and a clinical hold is to be imposed, the division director or acting director must be specifically involved. The reviewing medical officer may also discuss the protocol and possible revisions of it with the sponsor but the medical team leader must participate

in this discussion.

Communications with Sponsors

- Clinical holds of commercial INDs should be communicated to the appropriate sponsor representative by a telephone call from the division director (or acting division director). Clinical holds of individual investigator INDs should be communicated to the sponsor by a telephone call from the division project manager.

- For both commercial and individual investigator INDs, a letter describing the reasons for the clinical hold will be sent to the sponsor within 5 working days of the telephone call by which the clinical hold was communicated to the sponsor. This letter must bear the signature of the division director or acting division director.

Tracking

CDER will maintain a monthly tracking system to track IND submissions, IND clinical holds, and IND clinical hold releases. A print out of such actions will be sent on a monthly basis to: Office of Review Management (ORM) Office Directors, ADRAs/Special Assistants, Division Directors, Supervisory Project Managers, the Center Senior Project Manager, and Office of Pharmaceutical Sciences (OPS) Office of New Drug Chemistry (ONDC) Office Director and Division Directors, and Office of Biopharmaceutical Sciences (OBS) Office Director and Division Directors.

Responses to Clinical Holds

- When the sponsor believes it has responded to all issues raised in the clinical hold letter, *i.e.*, that a complete response has been submitted to the Agency, the cover letter to the response should so state, and the reply from the sponsor should be identified clearly as an "IND CLINICAL HOLD RESPONSE." To facilitate timely review of the response, CDER should ask the sponsor to send the response by overnight mail to the division document room, with a copy of the cover letter to the division project manager responsible for the IND. This process for responding to a clinical hold should be clearly described in all clinical hold letters to sponsors so that they will know how to respond appropriately and most expeditiously. A standard paragraph will be developed to be added to each clinical hold letter sent to a sponsor to describe this process.

- CDER will respond to a sponsor's complete reply to an IND clinical hold within 30 calendar days of receipt of the sponsor's complete reply to all issues raised in the clinical hold.

- If the division does not complete review of a sponsor's complete response to a clinical hold within the 30 calendar days, the new drug review Division Director should telephone the sponsor and discuss the review progress to date and what is being done to facilitate completion of the review.

- If upon completion of the review of the sponsor's complete response to the clinical hold, the division concludes that the drug should remain on clinical hold, the division director should call the sponsor and communicate the division's perspective on the matter. In these cases, the division director will also submit the IND for further review by the office director.

GENERAL REVIEW PRINCIPLES

- It is generally unhelpful to sponsors and a waste of CDER resources to perform Phase 1 IND reviews such that long lists of "NDA-type" deficiencies are sent to sponsors. Sponsors can be assumed to realize that the NDA submission must be more detailed than an initial IND submission. Identification of items that need to be addressed prior to submission of an NDA, but which are not needed to determine the safety of a proposed trial, is usually not necessary or appropriate for a Phase 1 IND review. This does not suggest that developing the manufacturing and controls aspects of a drug is not important during the IND phase or that potentially troublesome aspects of manufacturing and controls submissions should not be identified when detected. Sponsors should generally be encouraged to schedule End-of-Phase 2 meetings at which such specific issues can be more appropriately discussed. An exception to this general policy would be for a drug whose first U.S. submission occurs late in development or for drugs likely to have wide early use under expanded access programs.

- The review of an IND from a manufacturing perspective should concentrate on determining if there are any reasons to believe the manufacturing or controls for the clinical trial product present unreasonable health risks to the subjects in the initial IND trials. Such risks could arise from, for example, 1) a product made with unknown or impure components; 2) a product possessing chemical structures of known or highly likely toxicity; 3) a

product that cannot remain chemically stable throughout the testing program proposed; 4) a product with an impurity profile indicative of a potential health hazard or an impurity profile insufficiently defined to assess a potential health hazard; or 5) a poorly characterized master or working cell bank.

- In reviewing Phase 1 INDs, chemistry, biopharmaceutic, medical, statistical, microbiologic, and pharmacology/toxicologic reviewers ordinarily should not request data in addition to those listed in the "Guidance for Industry: Content and Format of Phase 1 Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-Derived Products." If a reviewer believes information not discussed in the Guidance is needed, this should be discussed first with **the appropriate discipline team leader** and with **the division director** before a request is made of a sponsor. That such consultation with both the team leader and the division director has taken place should be made clear to sponsors at the time any such additional request for information for a Phase 1 IND is made. All requests to the sponsor for such approved additional data should be made either by the project manager or by the involved reviewer along with the project manager. Documentation of such requests, including the reasons for the request, shall be included in the IND file.

RESPONSIBILITIES AND PROCEDURES

- **Recommending a Clinical Hold (Complete or Partial)**

  Internal discussions of INDs and the possible need for a clinical hold would ordinarily occur during one or more meetings of reviewers involved in the IND review. The various responsibilities outlined in this document are only for purposes of delineating responsibility. There is no implication that these events should occur as separate or sequential events.

  1. Primary Chemistry, Toxicology, Microbiology, Biopharmaceutic, Statistical, and Medical Reviewers will:

  Clearly note any recommendation for a clinical hold and the reasons for that recommendation in their IND review.

  2. Discipline Team Leaders will:

Clearly note concurrence or disagreement with the primary reviewer's recommendation(s) and the reason(s) for concurrence or disagreement.

3. Consumer Safety Officers (CSOs)/Project Managers (PMs) will:

a. Forward the recommendations of both the primary reviewer and the team leader to the division director for input into the decision on issuing a clinical hold.

b. Place a copy of the IND hold recommendation documents in the IND file.

4. Division Directors will:

Make the final decision on whether to issue a clinical hold. They will also assure that a clear record is created, signed, or initialed by the division director which documents the basis for the clinical hold, referencing specific discipline reviews, meetings, or other bases for the clinical hold.

- **Issuing a Clinical Hold (Complete or Partial)**

1. Division Directors will:

a. If a clinical hold is to be placed on a commercial IND, call the appropriate sponsor representative and inform the sponsor that the IND has been placed on clinical hold. The reasons for the hold should be discussed with the sponsor at the time the hold is imposed or, if the sponsor prefers, at a convenient time within the next several days when appropriate sponsor personnel are available to understand and discuss hold issues.

b. Assure that a memorandum of this teleconference is placed in the IND file and a copy is sent to the office director.

c. Assure that the office director is informed that the hold was placed and the reasons for the hold (by copy of memorandum of telecon) and that the IND file shows that the office director has been informed that the clinical hold has been placed *(e.g.*, included on cc list of memorandum of telecon).

d. At the request of the office director, discuss details of the clinical hold.

2. CSO/PMs will:

a. If a clinical hold for an individual investigator IND is to be issued, call the sponsor and inform them that the IND has been placed on clinical hold and offer to arrange a teleconference with the division director to discuss the hold.

b. For both commercial INDs and individual investigator INDs, assure that a letter, signed by the division director or acting division director, is sent to the sponsor detailing the reasons for the clinical hold within 5 working days from the day of the teleconference with the sponsor communicating the clinical hold. The primary purpose of this letter is to clearly identify the specific reasons for the clinical hold decision. Additional "non-hold" issues regarding the IND that the Division wishes to communicate to the sponsor should be sent to the sponsor in a separate letter or may be added to the end of the hold letter provided these are clearly marked as non-hold issues.

- **Monitoring Clinical Holds (Complete or Partial)**

1. The Reports Data Management Team will:

Provide monthly reports of IND submissions, IND clinical holds, and IND clinical hold releases to Office of Review Management (ORM) Office Directors, ADRAs/Special Assistants, Division Directors, Supervisory Project Managers, Center Senior Project Manager, and Office of Pharmaceutical Sciences (OPS) Office of New Drug Chemistry (ONDC) Office Director and Division Directors and Office of Biopharmaceutical Sciences (OBS) Office Director and Division Directors.

2. The New Drug Review Office Directors will:

Review at the next Divisional Administrative Rounds any clinical hold (complete or partial) that still remains in effect after 60 days. Reviews should continue until the hold(s) is (are) lifted.

- **Resolution of Clinical Holds/Acting on Sponsor Responses to a Clinical Hold:**

1. The Primary Reviewer(s) will:

Review the sponsor's complete response to the clinical hold and determine whether it resolves the reasons for the clinical hold. The reviewer will clearly document in the review of the response whether he/she believes the clinical hold should be lifted.

2. The Discipline Team Leader(s) will:

Review the primary reviewer's assessment of the sponsor's submission and clearly document whether the team leader concurs or disagrees with the primary reviewer with respect to the disposition of the clinical hold.

3. Division Directors will:

Decide within 30 days of receipt of the sponsor's complete response to the clinical hold whether the hold should be lifted. If the decision is TO NOT LIFT THE HOLD, the division director should telephone the sponsor and explain the division's perspective on the matter. A memorandum of telecon should be prepared and placed in the IND file. A letter describing the reasons for refusal to lift the hold should be sent to the sponsor within five business days. A copy of the letter, as well as the IND, should be submitted immediately to the office director for further review.

If the decision is TO LIFT THE HOLD, the division director should telephone the sponsor and inform it of this decision. A memorandum of telecon should be prepared and placed in the IND file. A letter confirming that the hold has been lifted should be sent to the sponsor within five business days. A copy of the letter should be sent to the office director.

4. Sponsors will:

a. Respond to a clinical hold usually by means of a submission to the IND in which there is either new data or new analysis or new explanation of why they consider the proposed clinical

study to be safe.

b. Have the option of appealing the clinical hold decision to the appropriate new drug review office director. However, there is ordinarily no need to appeal directly to the office director for scientific matters as review by the office will be automatic for any hold response considered inadequate by the review division to remove the clinical hold.

5. Office Directors will:

a. Review any instance in which a sponsor's response to a hold is considered inadequate by the new drug review division to remove the clinical hold.

b. Review any appeal by the sponsor.

c. Communicate the result of the review under 5a or 5b to the division by memo within ten business days after receipt of the IND hold package from the division. The office director will assure that a copy of this memo is placed in the IND file. If the office director concludes that the hold should be lifted, this should be communicated to a commercial sponsor by the division director and to an individual investigator sponsor by the CSO/PM that day. A memorandum of telecon should be prepared and placed in the IND file with a copy to the office director. Within five business days of the telecon a follow-up letter should be sent to the sponsor and placed in the IND file.

d. In the event the office director cannot complete the review under 5a or 5b in ten business days because of absence, the matter will be referred to either the Deputy Center Director for Review Management or the Center Director, who will then perform the duties of the office director in the matter.

6. The Clinical Holds Peer Review Committee will:

a. Meet quarterly to review all clinical holds (complete or partial) issued during the previous quarter (even if the IND clinical hold has been released prior to the meeting of the committee

b. Give sponsors the opportunity to appear before the committee when their IND is discussed and to offer their views, under proceedings similar to those used for the "refuse to file" review committee.

EFFECTIVE DATE

This guide is effective upon date of publication. Following the first year of operations under this guide, CDER will undertake a review of effectiveness of the various roles, responsibilities, and processes outlined in this guide. Based on the outcomes of that review, further changes in this guide may be necessary.